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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,977	02/26/1999	JAMES M. WILSON	GNVPN.019BUS	1765

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	20

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,977	WILSON ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-24 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-24 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Shukla, whereas any inquiries relating to formal matters should be directed to Ms. Pinkney, Patent Analyst. The phone numbers for Examiner Shukla and Patent Analyst Pinkney are provided at the end of this office action.

2. The request filed on 9-13-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/242,977 is acceptable and a CPA has been established. An action on the CPA follows.

3. Amendments filed 9-13-01 and the preliminary amendment filed 11-02-01 have been entered.

4. Claims 25 and 29 have been canceled.

5. Claims 18-24 and 26-28 are pending and are under current examination.

Claim Objections

6. Claim 22 is objected to because of the following informalities: "of" is missing between particles and rAAV. Appropriate correction is required.

7. Claim 28 is objected to because of the following informalities: "of" is missing between genomes and rAAV. Appropriate correction is required.

8. Claim 27 is objected because it recites the term "apoE" at one place and "ApoE" at another place. Applicants are advised to use one term consistently in all the claims at all the occurrences of the term.

Information Disclosure Statement

9. It is noted that the cite no. CX in the IDS filed 9-13-01 has been considered, however, a line has been crossed through it because it can not be printed as it is a pending US non-provisional patent application.

Drawings

10. It is noted that the drawing sheet for figure 13 does not have a label.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 18-24 and 26-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have amended claims 21 and 26 by introducing the embodiment "wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting....." which would encompass "equal to" or "less than" levels of contaminating adenoviral helper virus in claimed composition compared to the level of adenoviral helper virus contamination obtained after four rounds of cesium chloride centrifugation. However, the specification does not provide written support either for the phrase it self or for "less than levels of contaminating adenoviral helper virus". It is noted that Applicants in their response indicated to page 7, lines 25-34, page 9, lines 18-20, page 34, lines 19-20, and page 35, lines 1-2 for support of the amendment. However, none of the indicated sections of the specification disclose the recited phrase. Furthermore, none of the indicated sections of the specification disclose or define what would be encompassed by less than levels of adenoviral helper virus that would be obtained by subjecting recombinant AAV to four rounds of cesium chloride centrifugation. It is noted that the specification only discloses that the composition was subjected to four rounds of cesium chloride gradient centrifugation and there is no written support in the specification as what would be the contaminating levels of adenoviral helper virus after four rounds of cesium chloride centrifugation and artisan would not know what

contamination level would be considered to be no greater than contaminating levels of adenoviral helper virus in the recited composition when subjected to four rounds of cesium chloride gradient centrifugation.

13. Claims 18-24 and 26-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a recombinant adeno-associated virus (rAAV suspended in a biological compatible carrier, wherein the rAAV comprises (i) a 5' AAV inverted terminal repeat (ITR), (ii) a nucleic acid sequence encoding human apolipoprotein E (human ApoE) operably linked to a eukaryotic promoter, and (iii) a 3' ITR, and wherein the level of contaminating adenoviral helper virus is same as that obtained by subjecting said recombinant AAV to four rounds of cesium chloride centrifugation and a method of delivering ApoE to a patient in need of treatment of atherosclerosis, wherein said method comprises the step of administering to the patient intramuscularly the composition comprising the rAAV and wherein the ApoE encoding sequence in the composition is expressed in the patient and wherein a cytotoxic immune response directed against rAAV-transduced cells of the patient expressing ApoE is absent in the patient, does not reasonably provide enablement for any and all rAAV vectors wherein the ApoE encoding sequences are not linked to a promoter or wherein multiple ITRs or multiple ApoE encoding sequences are present or wherein the contaminating levels of adenoviral helper virus are lower than the levels of contaminating adenoviral helper virus after subjecting the rAAV to four rounds of cesium chloride centrifugation or wherein the vector is administrated by any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement

requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention encompasses rAAV wherein the ApoE encoding sequences are not linked to a promoter or wherein multiple ITRs or multiple ApoE encoding sequences are present or wherein the contaminating levels of adenoviral helper virus are lower than the levels of contaminating adenoviral helper virus after subjecting the rAAV to four rounds of cesium chloride centrifugation. However, the specification as filed is not enabling for the claimed invention commensurate with the scope of the claims because the specification does not provide sufficient guidance as to how an artisan of skill would have practiced the claimed invention and the artisan would have required extensive experimentation to make the viruses embraced by the scope of the claims and such experimentation would have been considered undue because the method of making and using such vectors was not routine in the art and the art of delivering protein in vivo was unpredictable.

The specification on page 9 discloses that a recombinant AAV vector carries a selected transgene and in addition the vector contains regulatory sequence that control the expression of the transgene in a host cell (see the last two sentences on page 9 continued on page 10). Further, the specification on page 10, lines 12, discloses that the vector is deleted of all the viral open reading frames and retains only 5' and 3' ITRs that are 143 nucleotides in length. While the specification notes

that the ITR can come from any AAV, there is no teaching in the specification as to how an artisan would have made an AAV vector with multiple 5' and 3' ITRs and multiple ApoE encoding sequence in the vector and no promoter. While it is noted that using molecular cloning techniques, an artisan could prepare a vector as recited in claims 21 or 26, an artisan would not have known how to use the vector in a patient or for the intended use of gene therapy or delivery. It is noted that at the time of the invention or even in year 2000, 5 years after the effective filing date of the claimed invention, it was not routine to make AAV vectors comprising multiple 5' and 3' ITRs and multiples copies of transgenes in a single vector and deliver the protein to a cell in vivo. Monahan et al reviewed the state of the art of AAV vectors in clinical use and stated,

"Unlike other delivery systems that have evolved into 1st, 2nd and even 3rd generation vectors, the rAAV original vector composition (145 bp terminal repeat constructs flanking the transgene of interest) appears to be the final version."

This indicates that the art did not teach AAV vectors with multiple ITRs. Regarding the issue of a transgene, Monahan et al used the term "transgene" for a cassette that consists of a promoter operably linked to the transgene of interest. In fact, they discuss in detail on page 25, first full paragraph, improvisation of the expression cassette by using different promoters, such as cell specific promoters. It should be noted that claim 18 of the instant application recites a vector wherein the vector comprises a promoter, which indicates that claim 21 was meant to encompass broad invention, which is without a promoter linked to the transgene. Furthermore, there is nothing in the specification to indicate that the transgene in the claim 21 as recited encompasses ApoE encoding sequences operably linked to a promoter. Accordingly, the specification does not provide any guidance as to how to use a recombinant AAV vector in which the transgene is not operably linked to a promoter. As discussed above, while an artisan could construct the vector, the artisan would not have been able to use vector in the intended method of gene therapy because the method of gene therapy in general is unpredictable.

In an assessment of the gene therapy art at the time of the invention, Verma and Somia (Verma IM and Somia N. Nature 389: 239-242. 1997) noted " In

principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further add, " But the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions-remain formidable challenges" (see the abstract). Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see first and second paragraphs in col 1 on page 239).

Anderson (Anderson WF. Nature 392 (SUPP):25-30, 1998) notes that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols have been approved worldwide. He further adds, "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Next, regarding the issue of administration and absence of immune response, Monahan (Gene Therapy 7:24-30, 2000) noted, "A significant caveat to these conclusions is that the cellular immune response to rAAV appears to depend on the route of administration. Brockstedt et al32 have used rAAV encoding ovalbumin to look at CTL and antibody response in C57B1/6 mice following intraperitoneal, intravenous, subcutaneous, or intramuscular delivery. The intramuscular delivery was the only route that did not develop CTL responses, while all routes led to antibody production against the transgene and the vector." Therefore, an artisan would have expected to lack or absence of immune response only when the vector was administered by intramuscular route. Additionally, the specification only teaches the injection of the virus in the muscles (see page 35, lines 17-20, page 38, lines 28-30). The specification does not provide any guidance as to how an artisan of skill would have administered by any route other than intramuscular injection without producing immune response and as noted above even 4 years

after the filing date of the invention, the art did not teach as to how to administer AAV vector by any route other than intramuscular injection and in fact the cited art of Monahan et al teaches that other routes produce immune response. Therefore, an artisan of skill would have to carry out extensive experimentation to find conditions that would have not produced immune response and such experimentation would have been undue since such was not routine in the art at the time of the invention.

In conclusion, the art of gene therapy is highly unpredictable in general. Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect.

Regarding the issue of "the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant AAV to four rounds of cesium chloride centrifugation", applicants do not describe what level of contamination would be considered no greater than that obtained after recited centrifugation. The specification on page 7, lines 25-34, discloses the term "helper free purified (i.e., rAAV which is substantially free of contamination with adenovirus or wild-type AAV). On page 34, the specification again discloses the phrase "four rounds of cesium chloride", however, it does not provide what contaminations would be present in the preparation. Again, an artisan would not be able to produce the rAAV as claimed because the specification does not provide any guidance as to what contamination would be considered as less than that obtained with four fold cesium chloride centrifugation and while one could centrifuge several time without any guidance regarding the contamination, an artisan would have required undue experimentation to make and use the vector as recited.

Accordingly, as discussed above, the specification as filed does not provided sufficient guidance for an artisan of skill to have made and used the claimed invention without undue experimentation and therefore, limiting the scope of the

claimed invention to a composition comprising a recombinant adeno-associated virus (rAAV suspended in a biological compatible carrier, wherein the rAAV comprises (i) a 5' AAV inverted terminal repeat (ITR), (ii) a nucleic acid sequence encoding human apolipoprotein E (human ApoE) operably linked to a eukaryotic promoter, and (iii) a 3' ITR, and wherein the level of contaminating adenoviral helper virus is same as that obtained by subjecting said recombinant AAV to four rounds of cesium chloride centrifugation and a method of delivering ApoE to a patient in need of treatment of atherosclerosis, wherein said method comprises the step of administering to the patient intramuscularly the composition comprising the rAAV and wherein the ApoE encoding sequence in the composition is expressed in the patient and wherein a cytotoxic immune response directed against rAAV-transduced cells of the patient expressing ApoE is absent in the patient, is proper.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 18-24, and 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 and 19 recite the limitation "the rAAV" in line 2. There is insufficient antecedent basis for this limitation in the claim because the term "a rAAV or rAAV" has not been recited in these claims before or in the base claim 21.

Claims 22-24 and 28 are vague and indefinite because they recite the term "genomes of rAAV". It is noted that these claims are dependent on claims 21 and 26, however, these claims do not recite "a rAAV", rather they recite the term "a recombinant adeno-associated virus (AAV)." Therefore, recitation of the term "the recombinant adeno-associated virus" in claims 22-24 and 28 is suggested. Alternatively, the recitation of the term "rAAV" in claims 21 and 26 and "the rAAV" in claims 22-24 and 28 is suggested.

Claims 21 and 26 are vague and indefinite because it recites the phrase "wherein the level of contaminating adenoviral helper virus is not greater than that obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation." It is noted that the specification does not disclose what would be considered the contaminating levels of adenoviral helper virus in the recited recombinant AAV composition of claims 21 and 26 and therefore, the metes and bounds of the claimed invention are not clear.

Claim 27 is indefinite because it recites the phrase "wherein the ApoE is administered intramuscularly." However the method of claim 26 recites administration of a recombinant AAV vector, not ApoE.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. The obviousness-type double patenting rejection of claims 18-24 and 26-28, set forth in the previous office action of 6-21-00 over claims 1-4 of US Patent 5,866,522 is maintained. Applicants' request that this rejection be deferred until allowance is acknowledged.

17. Claims 18-24 and 26-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-11 of co-pending Application No. 09/757,6673. Although the conflicting

claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for expressing a transgene (ApoE in the instant application) in an animal or in a cell or in a patient by introducing a composition comprising an adeno-associated viral vector comprising a transgene (ApoE encoding transgene in the instant application) into the cell such that the transgene is expressed in the cell, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the instant application recite characteristic of the adeno-associated viral composition as prepared by four rounds of cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector because both the applications disclose four rounds of cesium chloride gradient centrifugation for the adeno-associated virus composition. As such, the claims of the co-pending application 09/757,673 make obvious the instantly claimed method and AAV vectors comprising the ApoE gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 18-24 and 26-28 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9, 20, 21, 23, 25, 26, and 27 of co-pending Application No. 09/237,064. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method for expressing a ApoE in an animal/patient by introducing a composition comprising an adeno-associated viral vector comprising ApoE transgene into the cell such that the transgene is expressed in the cell, wherein the adeno-associated viral vector is free of helper adenovirus contamination. It is noted that although the claims of the instant application recite characteristic of the adeno-associated viral composition as prepared by cesium chloride centrifugation, this limitation would still encompass a composition free of helper adenovirus vector. As such, the claims of the co-pending application 09/237,064 make obvious the instantly claimed method and AAV vectors comprising the ApoE gene.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 18-24 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Podsakoff et al (US 5,858,351, 1-12-1999, filing date 1-18-1996) in view of Kashyap et al. (Ref CV of Paper No. 11).

Podsakoff et al teach a rAAV for gene therapy wherein the gene encoding erythropoietin is under the control of the CMV immediate early promoter, has SV40 polyadenylation sequences at the 3' end, and these sequences are flanked by 5' and 3' AAV ITRs (see materials and methods section in col 16 continued in col 17. They also teach that RSV promoter and other promoters can also be used for driving the expression of the gene of interest. They teach to purify the rAAV preparation by cesium chloride isopyknic gradient centrifugation and isolating the bands with average density of approximately 1.38 g/ml. Podsakoff et al also teach to inject the rAAV vector in mice intramuscularly in heart and cardiac muscles (see col 19 continued in col 20) and that erythropoietin is secreted by the myotubes or myoblasts. Podsakoff further teach that EPO gene was used as an example and that other suitable DNA sequences could be used that encode for proteins used for the treatment of different diseases (see lines 31-67 in column 10). Podsakoff et al does not teach an rAAV vector composition comprising 5' ITR, nucleic acid sequence encoding ApoE, and 3'ITR, wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant rAAV to four rounds of cesium chloride centrifugation.

Kashyap et al teach that genetic dyslipoproteinemias are ideal candidates for gene therapy since the molecular defects in the genes have been established and many of the diseases have significant sequelae to warrant treatment including premature cardiovascular and peripheral vascular disease or recurrent pancreatitis and pancreatic insufficiency (see the first paragraph in the section on discussion on page 1618). These investigators selected the apoE-deficient model to determine the feasibility of apolipoprotein gene replacement and prevention of atherosclerosis in mice with ApoE deficiency by providing the mice with an ApoE adenoviral vector intravenously. They also teach an ApoE adenoviral vector from which ApoE cDNA can be spliced out (see methods section on page 1613).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the rAAV vector of Podsakoff et al by cloning the ApoE cDNA taught by Kashyap et al e al, produce composition of the virus, purify it be cesium chloride centrifugation and use the resultant composition for delivery of ApoE gene to animals with reasonable expectation of success because all the pertinent methods are taught by Podsakoff et al and the cDNA for ApoE is taught by Kashyap et al. An artisan would have been motivated to use rAAV based method for ApoE gene delivery to treat atherosclerosis because Podsakoff et all teach that rAAV vector method is unique because of its ability to transduce non-proliferating cells along with the attributes of being inherently defective and nonpathogenic and because it is art recognized that adenovirus mediated gene delivery causes immune response (see lines 50-67 in column 1 of Podsakoff et al). With regard to claim limitations directed to specific titers of rAAV, it is noted that such an embodiment is sufficiently made obvious by the cited prior art of record in light of the state of the art as well as the level of skill of those in the art with regard to optimization parameters. For example, Podsakoff et al. teach the determination of effective dose range for rAAV vectors in Example 1. In particular, in Example 4, Podsakoff et al. teach i.m. injection into mice of rAAV-hEPO at 3×10^{11} vector genomes.

Response to Arguments

Applicant's arguments with respect to claim 18-24 and 26-28 have been considered but are moot in view of the new ground(s) of rejection. However,

Applicants arguments as they apply to the new rejection have been responded to. Applicants have amended the claims to recite the embodiment "wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant rAAV to four rounds of cesium chloride centrifugation", however, there is no recitation of what the contamination is or what is the level of contamination. Accordingly, the difference between the recited composition and the rAAV vector purified in Podsakoff et al can not be ascertained. Furthermore, on page 34, lines 22-24, the AAV particles purified according to the method described in the specification (four rounds of cesium chloride centrifugation) had a density of 1.37-1.40 g/ml. The AAV composition purified by the method of Podsakoff et al has a density of 1.38 g/ml (see lines 20-35 in column 18, particularly line 30-32). Therefore, by one characteristic disclosed in the specification the composition of Podsakoff et al and the instant invention would have the same level of contamination. Therefore, applicants' arguments that Podsakoff et al does not teach or suggest a composition comprising rAAV in which the level of contaminating adenoviral helper virus is no greater than is obtained by subjecting the rAAV to four rounds of cesium chloride is not persuasive. Applicant's arguments that heating and inactivation does not affect the antigenicity of the adenoviral vector are irrelevant because none of these conditions are recited in the claim. Furthermore, it is noted that the claim does not recite a composition prepared by four rounds of cesium chloride centrifugation, rather it recites a compositions that has certain characteristics and therefore, any composition that possesses the same characteristics as those describe in the specification for the recited composition would read on the claimed composition. It is reiterated that the rejection of record is entirely made on the basis of the construction of a rAAV vector and not with regard to the intended use of the vector *in vivo*. The claims, as written, fail to recite any limitations, which distinguish the claimed product over the prior art product. The specific purification protocol is irrelevant to the claimed product unless the protocol results in a distinguished product over the prior art product.

21. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c) and a copy of all the pending/under consideration claims. For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA, PH.D
PATENT EXAMINER